POROUS CHITOSAN-DRUG FORMULATIONS BY $SCCO_2$-ASSISTED ATOMIZATION

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This work aims to produce porous biopolymer particles for pharmaceutical applications. In particular chitosan and chitosan ibuprofen-loaded particles are being produced through supercritical CO_2-assisted atomization in a SAA laboratory scale apparatus at NOVA and in a pilot scale PGSS drying apparatus at BOCHUM.
Particles were obtained in the range of 2 μm to around 1 mm. Chitosan particles were further impregnated in a batch reactor in $scCO_2$ and the drug uptake and release profiles compared with the chitosan-ibuprofen co-atomization formulation. The drug release profiles were evaluated by *in vitro* experiments at PBS pH 7.4 and 37 ºC.
Preliminary results show that the way of loading the particles influence both the impregnation degree of the drug and the release profiles of the formulations.

INTRODUCTION

Chitosan is a nontoxic, biodegradable and biocompatible polymer that has received increasing attention as a renewable polymeric material. These properties turn chitosan particularly suitable for biomedical and pharmaceutical formulations. Chitosan can be used as excipient, binder, granulating agent in ground mixtures, co-grinding agent for dissolution rate and bioavailability enhancement of water insoluble drugs, etc. Due to its mucoadhesive properties it has been extensively investigated in the development of controlled drug delivery systems for nasal and oral delivery of polar drugs, to include peptides and proteins for vaccine delivery.[1,2,3]
Supercritical fluid technology has an enormous potential in the synthesis and processing of materials and formulations for biomedical and pharmaceutical applications, where controlled morphology and purity are key parameters.
Only few works on processing chitosan using supercritical fluid technology have been reported in literature, mainly due to the difficulty of dissolving chitosan. [4,5]
This work is part of a MIT-Portugal Program funded project which aims to develop porous particles to lung-targeted drug delivery and also in the aim of NOVA-Bochum collaboration through a Luso-German Bilateral Agreement.
A laboratory scale SAA apparatus and a pilot scale PGSS drying apparatus are being used in the preparation of porous bio-polymers-drug formulations, covering a wide range of CO_2 flows and liquid compositions. The solvent composition of the polymeric liquid flow is one of the parameters that is being studied at the moment in order to tune the specific characteristics of the particles, such as high porosity and density.

EXPERIMENTAL AND CONCLUSIONS

Process parameters such as precipitator temperature, chitosan solution concentration, CO_2 flow, liquid/CO_2 flow ratio and atomization nozzle diameter are key parameters that can influence on the morphology, density and particle size of the precipitated particles.

Two approaches were followed to obtain drug/chitosan formulations: i) Ibuprofen, used as a model drug, was dissolved in the liquid solution and co-precipitated with chitosan; ii) Chitosan particles were further loaded with ibuprofen by scCO_2-assisted impregnation in a batch high-pressure cell. The drug release profiles were evaluated by *in vitro* experiments at PBS pH 7.4 and 37 ºC. Quantification was performed by UV spectroscopy.

Figures 1 and 2 show the experimental apparatus used at both research centers.

Fig 1. SAA apparatus at NOVA

Fig 2. PGSS-drying plant at BOCHUM

Figure 3 shows examples of SEM images of particles obtained at both laboratories. The SAA lab scale apparatus is equipped with a 150 µm nozzle and is operating with a CO_2 flow rate of 1.5 Kg/hour while the PGSS apparatus is working with a nozzle of 1.2 mm of diameter and CO_2 flow rates up to 100 Kg/hour. The concentration of chitosan in the acidic liquid stream suitable for atomization must be up to 2 wt%. Higher concentrations lead to extremely viscous solutions.

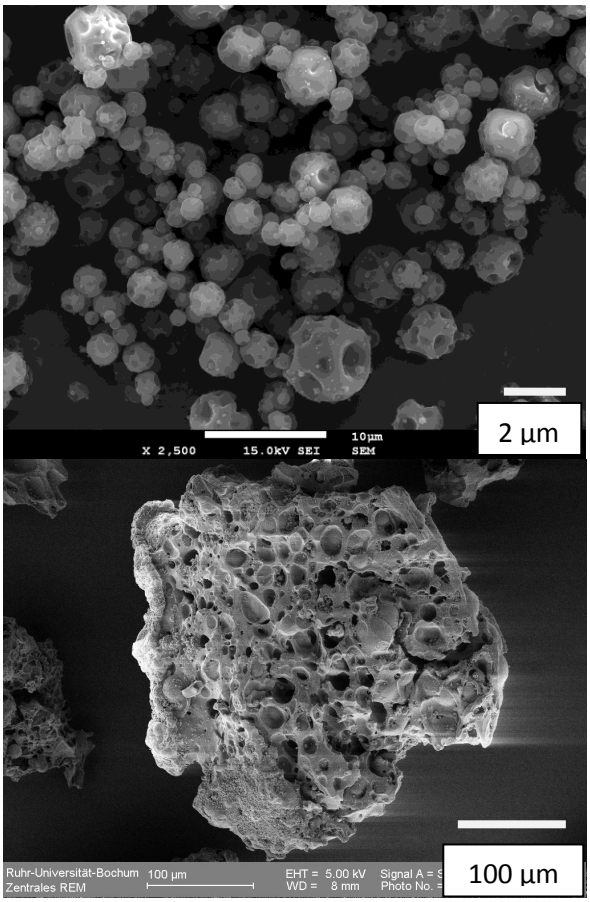

Fig. 3. SEM images of chitosan particles produced at (A) NOVA apparatus and (B) BOCHUM plant.

SEM images show that the particles obtained at NOVA are quite mono disperse in size (around 2 µm), discrete and spherically shaped with holes at the surface due to shrinking during the drying of the particles. Particles obtained at Bochum are much bigger particles ranging from 200 µm to 1mm, with very irregular structure but showing extremely porous surfaces envisaging interesting biomedical applications.

Impregnation of chitosan particles obtained in both apparatus was performed at 65 ºC and 20 MPa for 20 hours, in a high-pressure cell equipped with sapphire windows. A porous net divides the cell in two compartments in order to prevent physical contact between the drug and the samples. Ibuprofen was placed in the bottom compartment, with a magnetic stirrer bar, and in enough quantity to obtain medium saturation at the *p*,

T impregnation conditions. The polymers were loaded into cellulose membranes (cutoff 3.5KDa) which were placed in the top compartment of the cell. At the end of the impregnation period the system was quickly depressurized.

Figure 4 shows the cumulative amount of ibuprofen release profiles from both chitosan and chitosan/ ibuprofen particles pH 7.4, 37ºC for 25 hours.

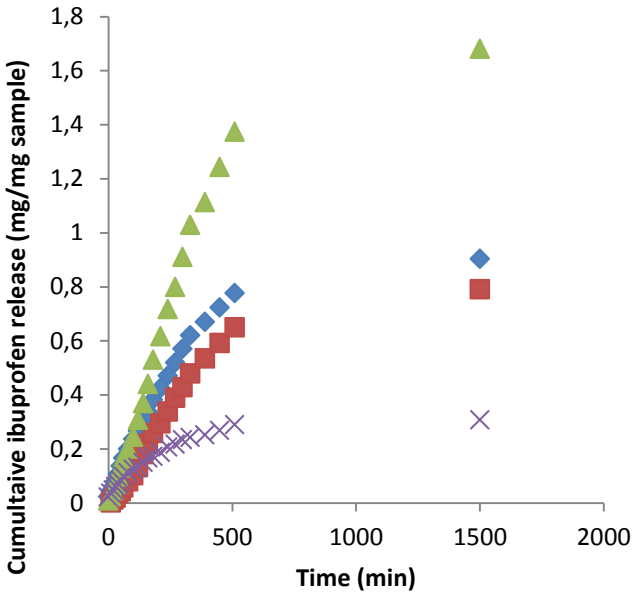

Fig. 4. Cumulative ibuprofen release. NOVA: (■) impregnated and (◊) co-atomization and BOCHUM: (▲) impregnated and (X) co-atomization.

As is can be seen in Figure 4 there are quite distinct differences in the ibuprofen loading of the particles. While the particles produced at NOVA show quite similar cumulative releases, with the co-atomized particles showing just slightly higher ibuprofen content, the particles produced at BOCHUM show a very pronounced difference with the particles impregnated showing a much higher ibuprofen loading (~1.7 mg/g sample) than the particles resulting from co-atomization (~0.3 mg/g).

Figure 5 shows the experimental release profiles of ibuprofen from the particles in a PBS solution at 37ºC and pH 7.4 at sink conditions.

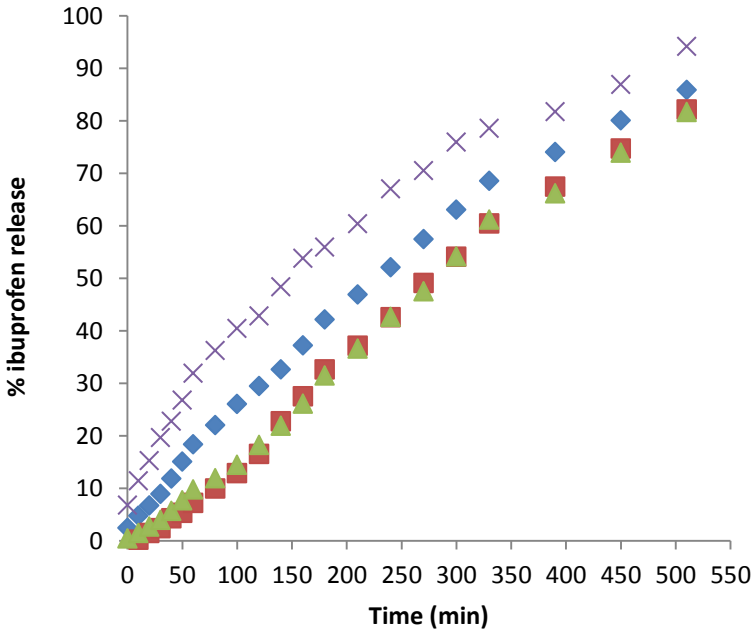

Fig. 5. *In vitro* release profiles of ibuprofen from chitosan and chitosan/ibuprofen particles at 37ºC and pH 7.4 PBS, for 9 hours. NOVA: (■) impregnated and (◊) co-atomization and BOCHUM: (▲) impregnated and (X) co-atomization.

From figure 5 it is possible to observe that the formulations obtained from the posterior impregnation of the particles in $scCO_2$ present faster drug releases than the ones obtained by co-atomization. This might be explained by the location of the drug more at the surface in the drying process during the atomization while during the $scCO_2$-assisted impregnation the high diffusivity of CO_2 followed by rapid depressurization can load the drug inside the particles which are hollow. The faster ibuprofen release was obtained from the particles obtained at Bochum from co-atomization followed by the co-atomization at NOVA. These significant differences in the co-atomization profiles could be related with the morphology and porosity of the particles. The faster release from BOCHUM particles is related with a higher surface area due to a much pronounced irregularity of the particles and higher porosity.

CONCLUSIONS

This work is focused on the development and optimization of biopolymer porous particles using synergies from NOVA and BOCHUM groups. While the production of particles by atomization is an already well-established technique, the optimization of the formulations is still a challenge with many available variables that can be tuned and optimized in order to increase their applicability in the pharmaceutical and biomedical industries.

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